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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/727,509	10/22/96	DARZYNKIEWICZ	1075-PCT.

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HM31/0428

EXAMINER

SIEU, J

ART UNIT

1634

PAPER NUMBER

DATE MAILED:

04/28/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
**08/727,509**

Applicant(s)  
**Zbigniew Darzynkiewicz et al.**

Examiner  
**Jeffrey Siew**

Group Art Unit  
**1634**



☒ Responsive to communication(s) filed on 9 Feb 1998

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-20 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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## **DETAILED ACTION**

### ***Location of Application***

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634, and is assigned to Patent Examiner Jeffrey Siew.

### ***Information Disclosure Statement***

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### ***Specification***

3. The use of the trademark TRITON X-100 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

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4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Acknowledgment is made of applicant's intent to file an abstract via a Supplemental Amendment. Upon review of the file, however, no Supplemental Amendment has been made of record.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY THE AMENDMENT

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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6. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczyca et al. (Cancer Research 53 1945-1952, April 15, 1993), in view of Vanderlaan et al. (US PAT 5053336, Oct 1, 1991), and Xun Li et al. ( Int. J. Of Oncology 1157-1161, 1994).

These claims are drawn to a method of labeling of nuclear DNA strand ends with halogenated nucleotides and in situ detection in cells by a labeled antibody . Gorczyca et al. teach the detection of DNA strand breaks in apoptotic cells. Using terminal deoxynucleotidyl transferase (TdT), the ends of nuclear DNA strand breaks were labeled with biotinylated dUTP in apoptotic cells and subsequently detected in situ with labeled antibodies (see page 1, line 3 abstract).

Gorczyca et al. do not teach the use of halogenated nucleotides as a label.

Vanderlaan et al. teach the detection of halogenated nucleotides that were bound during normal DNA synthesis, using monoclonal antibodies specific to these halogenated nucleotides (see column 9, line 40) . Vanderlaan et al. do not teach end labeling of DNA strand breaks with these halogenated nucleotides. This method does require a denaturation step for a labeled monoclonal antibody to bind to incorporated halogenated nucleotides.

Xun Li et al. teach the use of 5-bromo-2-deoxyuridine for the photolysis of DNA and that the breakage of DNA strands can be detected by biotin labeled nucleotides, catalyzed by TdT. The strand breaks of the DNA were generated by photolysis and eliminated the denaturation step (see page 1158, Materials and Methods).

One of ordinary skill in the art would have been motivated to apply the teachings of Vanderlaan regarding the labeling with halogenated nucleotides and detection with antibodies thereto

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in the assay of Gorczyca. Gorczyca taught that using terminal deoxynucleotidyl transferase, broken 3' ends of DNA strands bind with a labeled nucleotide. Vanderlaan taught that a halogenated nucleotide binds to the 3' end of DNA strands during extension in normal DNA synthesis. It would have been expected that the halogenated nucleotides that incorporate into 3' end of DNA strands during normal DNA synthesis would also bind to the 3' end of broken DNA strands of apoptic cells as shown by Gorczyca. Xun Li et al. further teaches the use of halogenated nucleotides to break the DNA strands to eliminate the need for denaturation and the subsequent use of labeled nucleotides to detect those breaks. The precondition of broken DNA strands caused by either photolysis or apoptosis actually eliminated the denaturation step. Once the DNA strands were broken, regardless of the means by which those strands were broken, it would have been prima facie obvious that one of ordinary skill in the art to carry out labeling with halogenated nucleotides on the resulting DNA strand breaks.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the

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date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### *Conclusion*

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is jsiew@uspto.gov. The examiner can normally be reached on Monday through Friday from 6:30 a.m. to 3 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone numbers for Group 1630 are (703) 305-3014 and (703) 305-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist for Technology Center 1600 whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing

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of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The CMI Fax Center numbers for Group 1600 are (703) 305-3014 and 305-4227.

4/27/98  
*J. Siew*

KENNETH R. HORLICK  
PRIMARY EXAMINER  
GROUP ~~1600~~ 1600 4/27/98  
*Kenneth R. Horlick*